Remarks/Argument

Claims 45-77 and 96-100 are pending in the application. Claims 45, 59, 97, 98 and 100 have been amended. Support for amended claim 45 is found on pg. 11, ln. 15 of the specification. Support for amended claim amended claim 59 is found on pg. 14, lns. 8-9 of the specification. Support for amended claim 97 is found on pg. 14, lns. 13-14 of the specification. No new matter has been added by these amendments.

New claims 101-103 are presented. Support for new claims 101 and 102 is found on pg. 11, ln. 17 to pg. 12, ln. 4 and on pg. 12, ln. 14 to pg. 13, ln. 2 of the specification, respectively. Support for new claim 103 is found on pgs. 28-30 of the specification. No new matter has been added.

Upon entry of this amendment, claims 45-77 and 96-103 will be pending. The Applicant believes that the above amendments and additions, and the remark/arguments presented below, put the claims in better condition for allowance or for appeal. The Applicant therefore respectfully requests entry of this response, and reconsideration of the claims.

The Applicant's representative thanks Examiner Kam for discussing this case by telephone on July 27, 2004. During that discussion, Examiner Kam indicated that she would consider new claims which recite specific embodiments of the present medicaments (that is, new claims 101-103), and a Declaration by Applicant, Leonard Girsh, M.D., which shows treatment of a patient with a medicament of the invention. The Declaration of Dr. Leonard Girsh is submitted herewith.

Response to section 112, 2nd paragraph rejections

Claims 45-77 and 96-100 are rejected under 35 USC 112, 2nd paragraph as allegedly being indefinite for reciting the phrase "when healthy, by a characteristic amino acid molar ratio for the healthy tissue per se, or for at least one peptide, polypeptide or protein thereof." Claim 45 has been amended to remove this phrase, and to recite that the ratio of the plurality of L-amino acids in the claimed medicament is characteristic of healthy tissue of the type being treated for damage.

The characteristic amino acid ratio in the claimed medicaments will vary from tissue to tissue, as would be readily understood by one of ordinary skill in the art. Section 4 of the present specification, on pgs. 32-34, discloses that the skilled physician can collect healthy and diseased tissue samples and readily determine their amino acid composition. Exemplary and art-recognized techniques for determining the amino acid (and other chemical) composition of tissues, such as Coomassie blue staining or MRI spectroscopic analysis, are discussed in this Section 4. (The determination of tissue chemical composition will be discussed in more detail in the section titled Response to section 112, 1st paragraph enablement rejection below.)

Moreover, the use of a variable claim term does not necessarily render that claim indefinite, as long as one skilled in the art would understand what is claimed in light of the specification. MPEP 2173.05(b). Here, one skilled in the art would immediately recognize that different tissues have different amino acid and other chemical compositions, and that the different amino acid and chemical compositions could be readily ascertained by techniques within the skill in the art. Claim 45 (and its dependent claims 46-77 and 96-100) are therefore clear and definite. The Applicant respectfully requests that the 35 USC 112, 2nd paragraph rejection of these claims be withdrawn.

New claims 101-102 have been added which specify L-amino acid ratios for skin and blood, respectively. As the amino acid ratios in claims 101-102 are explicitly stated, these claims are believed to be clear and definite. New claim 103 specifies that the damaged tissue is selected from the group consisting of skin, hair, nails, teeth, eye, liver, gastro-intestinal, kidney, lung, connective tissue, stem cells and HIV-damaged tissue. As discussed above, one skilled in the art would immediately recognize that the tissues recited in claim 103 would have different amino acid (and other chemical) compositions, and that these compositions can be readily determined by well-known techniques. Thus, claim 103 is also clear and definite.

Claims 56, 57 and 61-64 are rejected under 35 USC 112, 2nd paragraph as allegedly indefinite for reciting that the claimed aliphatic side chain is a fatty acid. According to the Examiner, aliphatic side chains do not have carboxylic acid groups, whereas fatty acids do. Therefore, the claimed aliphatic side chain allegedly cannot be a fatty acid.

The word "aliphatic" is an adjective describing the chemical side chain recited in claim 55 (from which claims 56, 57 and 61-64 depend). As stated in Morrison RT and Boyd RN, Organic Chemistry, 4th Edit. Allyn and Bacon, Inc., Newtown, MA, 1983, p. 573 (attached), an aliphatic compound is an "open chain compound," and "the original meaning of the word() 'aliphatic (fatty) . . . no longer (has) any meaning." Thus, one skilled in the art would understand that a fatty acid, which is an open-chain compound, can be aliphatic regardless of the presence of a carboxylic acid group. Claims 56, 57 and 61-64 are therefore clear and definite, and the Applicant respectfully requests that the 35 USC 112, 2nd paragraph of these claims be withdrawn.

Claim 97 is rejected under 35 USC 112, 2nd paragraph as allegedly being indefinite for reciting "L-gamma aminobutyric acid." This claim has been amended to read "gamma aminobutyric acid," and the Applicant respectfully requests that the indefiniteness rejection of this claim be withdrawn. Claim 99 has also been amended to change "L-betaine" to "betaine."

Claims 98 and 100 are rejected under 35 USC 112, 2nd paragraph as allegedly being indefinite for reciting "or and." The word "or" has been deleted from these claims in this context, to indicate that the claim recites a Markush group. The Applicant respectfully requests that the 35 USC 112, 2nd paragraph rejection of claims 98 and 100 be withdrawn.

Response to section 112, 1st paragraph enablement rejection

Claims 45-77 and 96-100 are rejected under 35 USC 112, 1st paragraph as allegedly being non-enabled for an anabolic medicament for treating damaged tissue comprising at least one mucopolysaccharide compound in an amount which is effective to act as an anti-neo-inflammatory and anti-neo-angiogenetic agent; at least one polar surface active lipid; and a plurality of amino acids, no more than 10% of which are in the D-form, in a molar ratio which is characteristic in healthy tissue of the type being treated for damage. The Applicant respectfully traverses the rejection.

According to the Examiner, the present specification provides no guidance regarding the molar ratio of amino acids in the claimed compositions for treatment of damage to a given tissue.

The Examiner also contends that the claims encompass "unspecified variants regarding the identities and amounts of components in the anabolic composition," and that the effects of the claimed compositions on damaged tissue are not adequately described. Finally, the Examiner contends that "the specification has not shown the effect of the (claimed) anabolic composition, especially in that no working examples have been provided, and that the effect of the claimed composition is "highly unpredictable."

The molar ratio of amino acids in a given tissue can, of course, differ from that in other tissues. This amino acid ratio can be readily determined by one skilled in the art without undue experimentation, by following the teachings of the specification and applying the knowledge possessed by the skilled person.

MPEP 2164.01(c) states that "it is not necessary to specify the dosage . . . if it is known to one skilled in the art that such information could be obtained without undue experimentation." If the experimentation required to find that dosage is routine, it is not considered "undue" even though such experimentation may be difficult or time-consuming. See, *e.g.*, MPEP 2164.06, quoting In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988), which states:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Thus, the time and difficulty of the experiments required to practice a claimed invention are not determinative of non-enablement if these experiments are "merely routine." MPEP 2164.06.

Here, sufficient guidance is provided in the specification to allow one skilled in the art to readily determine the molar ratios of L-amino acids in the claimed compositions with merely routine experimentation. For example, Section 4 on pgs. 32-34 of the present specification, titled "Individualized Therapy," discloses that "to optimize therapy with the present invention, an individual profile of each patient is compiled and stored." An individualized profile for a patient can be obtained by taking samples from that patient, such as by tissue biopsy (see pg. 33, lns. 19-21 of

the specification). As stated in the specification on pg. 32, lns. 19-23 and pg. 33, lns. 11-16, respectively:

> The information collected includes blood protein types, lipid levels, DNA sequence, nutrient component levels in the blood including the amino acid composition, and nutrient levels in the cells, tissue and organs. In particular, amino acid composition of organs and tissues is collected.
>
> Diseased tissue may be chemically analyzed and compared with healthy adjacent tissue to determine the nutrients needed using specially designed software. Nutrient-specific stains such as Coomassie blue may be employed to identify amino acids, proteins and other nutrients in tissue samples. MRI spectroscopic analysis and other analyses known to those of skill in the art may be used to determine tissue and cell chemical composition and thereby discover the deficient nutrients.

The specification at pg. 34, lns. 2-3 discloses that such other analyses for tissue nutrient composition include non-invasive methods, such as blood analysis, and analysis of secreted liquids. The information obtained from the tissue analyses is specifically used to determine the appropriate molar ratios of amino acids for use in the claimed compositions; see pg. 33, lns. 1-2 of the specification.

Furthermore, the specification identifies useful therapeutic applications for specific L-amino acids in Table 1 on pg. 22. As stated on pg. 21, lns. 15-22 of the specification:

> This additional information (in Table 1) may be useful in identifying specific cell or tissue proteins whose amino acid components can be mimicked in a therapeutic formulation of the invention. For example, tissues can be analyzed to locate high concentrations of specific amino acids known to favorably treat a specific ailment. From these tissues, specific proteins can be identified that are related to the ailment and the amino components of these proteins can be administered in one of the therapeutic formulations of the invention.

Thus, one skilled in the art can readily determine the appropriate molar ratios of L-amino acids for the claimed medicaments required to treat damage of a particular tissue, with no more than routine experimentation, by following the teachings of the specification.

The amount of at least one mucopolysaccharide compound which is effective to act as an anti-neo-inflammatory and anti-neo-angiogenetic agent, and the at least one polar surface active lipid

(which is also believed to have anti-inflammatory activity) can also be readily ascertained by one skilled in the art by monitoring the degree of inflammation in and around the tissue being treated. Techniques for monitoring tissue inflammation are well-known in the art. Exemplary amounts of the at least one mucopolysaccharide compound and the at least one polar surface active lipid for use in the claimed medicaments are given on pgs. 24-25 and in the working examples. Thus, appropriate amounts of the at least one mucopolysaccharide compound and the at least one polar surface active lipid for use in the claimed compounds can be identified by merely routine experimentation.

The Examiner cites to an alleged lack of working examples as showing that the present specification does not teach how to make and use the claimed medicaments. However, "the specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." MPEP 2164.02. As discussed above, the specification contains ample guidance to allow one skilled in the art to make and use the claimed medicaments.

In any event, Case 2 of the working examples (pg. 39 of the present specification) shows the prophetic treatment of an adult female kidney transplant patient with a medicament of the invention. The medicament of the invention identified in Case 2 comprises 4-5 capsules daily containing 390 to 500 mg L-amino acids, linoleic and linolenic fatty acid for a total amount of about 0.3 to 0.5 g per day, the antioxidant lipid EPA at about 0.3 to 0.5 g per day, and the extracellular matrix materials chondroitin sulfate, cartilage, and collagen in a total amount of about 1500 mg per day.

For ease of comparison to the elements appearing in claim 1 of the present application, the components of the composition used to treat the patient in Case 2 are listed below in terms of the language of claim 1.

Medicament from Case 2	**Claim 1**
chondroitin sulfate, cartilage, and collagen in a total amount of about 1500 mg	at least one mucopolysaccharide compound in an amount which is effective to act as an anti-neo-inflammatory and anti-neo-angiogenetic agent
linoleic and linolenic fatty acid for a total amount of about 0.3 to 0.5 g per day, the antioxidant lipid EPA at about 0.3 to 0.5 g per day	at least one polar surface active lipid

390 to 500 mg L-amino acids	a plurality of amino acids, no more than 10% of which are in the D-form, in a molar ratio which is characteristic in healthy tissue of the type being treated for damage

It is expected that, as a result of treatment with the claimed composition, the kidney transplant patient will be able to use reduced levels of antirejection medication (such as corticoids, macrolides, and cyclosporin) and thus reduce the onerous side effects from these medications. Should the patient require less medication after treatment with the claimed composition, the ordinarily skilled physician would conclude that repair of the tissue being treated had occurred.

The effect of the presently claimed medicaments is further illustrated in the attached Declaration submitted by the Applicant, Dr. Leonard Girsh, which shows the actual treatment of a 71-year-old female patient suffering from Crohn's disease. The Applicant administered to this patient a medicament according to the present invention, comprising about 10.6 g Neocate infant formula containing L-amino acids and glycine, in the genetic code and molar ratio of human tissue (breast milk and stem cell human tissue); about 50-100 mg lecithin; about 12.5-40 mg phosphatidyl choline; about 225 mg EPA from fish oil; 500 mg flaxseed oil (equivalent of about 275-325 mg linolenic acid); and extracellular matrix components comprising collagen, proteoglycan aggregate complex of cartilage and chondroitin sulfate (shark cartilage 740 mg per capsule, twice daily). As discussed in the Declaration, treatment with this composition caused a significant improvement in the Crohn's disease patient, and the patient was able to take a much-reduced dose of anti-inflammatory corticosteroids.

It was well-known at the time the present application was filed that a reduction in inflammation and the clearing of symptoms in Crohn's disease, such as those detailed in the declaration, are indicative of tissue healing. See paragraphs 9-10 of the Declaration. Moreover, the administration of the presently claimed medicaments encourage anabolism in the patient. As stated in the present application, at pg. 13, lns. 5-8 and at pg. 13, ln. 17 to pg. 14, ln. 1, respectively:

> [I]t is believed that the inventive therapeutic formulations work to promote tissue repair by providing stem cells with the optimal ratios and proper stereoisomer form of amino acids that are needed to synthesize new tissue . . .

> [B]y altering the balance of free L amino acids such that under the law of mass action, protein synthesis is favored over proteolysis. By adding additional free amino acids, the activity of enzymes involved in protein synthesis and degradation, such as proteases, is driven in the direction of protein synthesis and therefore in the direction of tissue production rather than protein degradation. Also, it is believed that the addition of L amino acids inhibits or arrests the catabolic protein degradation reactions of these enzymes.

Thus, as predicted in Case 2 of the working examples, and as proven by the treatment of the Crohn's disease patient presented in the Declaration, the claimed medicaments promote tissue healing by reducing inflammation while a the same time stimulating anabolic processes. These medicaments can be readily made and used by one skilled in the art, without undue experimentation.

Claims 45-77 and 96-100 are therefore enabled for an anabolic medicament for treating damaged tissue comprising at least one mucopolysaccharide compound in an amount which is effective to act as an anti-neo-inflammatory and anti-neo-angiogenetic agent; at least one polar surface active lipid; and a plurality of amino acids, no more than 10% of which are in the D-form, in a molar ratio which is characteristic in healthy tissue of the type being treated for damage. The Applicant respectfully requests that the 35 USC 112, 1st paragraph rejection of these claims be withdrawn.

Although one skilled in the art can readily determine the appropriate L-amino acid molar ratios for the claimed medicaments, specific L-amino acid molar ratios are disclosed in the specification. For example, a molar ratio of L-amino acids for treating damaged skin is given on pg. 11, ln. 17 to pg. 12, ln. 4 of the specification, and for treating blood clotting deficiencies is given on pg. 12, ln. 14 to pg. 13, ln. 2 of the specification. These represent the L-amino acid molar ratios of healthy skin and healthy blood, respectively. New dependent claims 101 and 102 have been added which separately recite these molar ratios. As the tissue type being treated and the L-amino acid molar ratios are expressly recited in new claims 101 and 102, these claims are enabled.

Pending claims 59, 60, 75, 99 and 100 specify that the L-amino acid ratio in the claimed medicament is that of cyclosporin. As disclosed on pg. 14, lns. 3-4, cyclosporin comprises nonpolar cyclic oligopeptides that have immunosuppressant activity. Page 14, lns. 8-9 disclose that a molar

L-amino acid ratio that produces cyclosporin effects is 2 moles L-valine; 4 moles L-leucine; and 2-moles L-alanine. These values have been inserted into claim 59 to more particularly point out and distinctly claim this subject matter; the scope of claim 59 has not been changed by this amendment. Because a molar L-amino acid ratio is expressly recited in claim 59, this claim and claims 60 and 75 (which depend from it) are enabled.

Claim 99 already expressly recites molar ratios of L-amino acids, and also of glycine, betaine, methionine and 4-aminobutyric acid. As disclosed on pg. 14, lns. 9-14, this represents a further embodiment in which the L-amino acid ratio in the claimed medicament is that of cyclosporin. Because a molar L-amino acid ratio is expressly recited in claim 99, this claim and claim 100 (which depends from it) are enabled.

New claim 103 specifies that the damaged tissue is selected from the group consisting of skin, hair, nails, teeth, eye, liver, gastro-intestinal, kidney, lung, connective tissue, stem cells and HIV-damaged tissue. As discussed above, one skilled in the art could readily determine the L-amino acid molar ratios required to make the presently claimed medicaments for treating damage to these tissue. In particular, the L-amino acid compositions in the presently claimed medicaments for treating damaged skin and blood (fibrinogen) are disclosed in the present specification at pg. 11, ln. 17 to pg. 12, ln. 4; and on pg. 12, ln. 14 to pg. 13, ln. 2, respectively. New claim 103 is therefore enabled.

Conclusion

Based on the foregoing, all claims are believed to be in condition for allowance. An early action toward that end is earnestly solicited.

Respectfully submitted,

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- Declaration of Leonard S. Girsh, M.D.

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14

Aromaticity

Benzene

14.1 Aliphatic and aromatic compounds

Chemists have found it useful to divide all organic compounds into two broad classes: **aliphatic** compounds and **aromatic** compounds. The original meanings of the words "aliphatic" (*fatty*) and "aromatic" (*fragrant*) no longer have any significance.

Aliphatic compounds are open-chain compounds and those cyclic compounds that resemble open-chain compounds. Except for the occasional appearance of a phenyl (C_6H_5) group, the hydrocarbon portions of the compounds that we have studied so far have been aliphatic.

Aromatic compounds *are benzene and compounds that resemble benzene in chemical behavior.* Aromatic properties are those properties of benzene that distinguish it from aliphatic hydrocarbons. The benzene molecule is a *ring*: a ring of a very special kind. There are certain compounds—other ring compounds—which seem to differ from benzene in structure, yet which behave very much like benzene. These other compounds, it turns out, actually do resemble benzene in structure—in basic electronic configuration—and they are aromatic, too.

Aliphatic hydrocarbons—alkanes, alkenes, alkynes, and their cyclic analogs—undergo chiefly addition and free-radical substitution: addition at multiple bonds, and free-radical substitution at other points along the aliphatic chain. These same reactions, as we have seen, take place in the hydrocarbon portions of other aliphatic compounds. The reactivity of these hydrocarbon portions is affected by the presence of other functional groups, and the reactivity of these other functional groups is affected by the presence of the hydrocarbon portions.

In contrast to aliphatic hydrocarbons, we shall find, *aromatic hydrocarbons are characterized by a tendency to undergo heterolytic substitution.* Furthermore, these same substitution reactions are characteristic of aromatic rings wherever they appear, regardless of other functional groups the molecule may contain. These other functional groups affect the reactivity of the aromatic rings, and the aromatic rings affect the reactivity of these other functional groups.